Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 16, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.11.050

YEAR IN CARDIOLOGY SERIES

The Year in Atherothrombosis

Javier Sanz, MD, Pedro R. Moreno, MD, FACC, Valentin Fuster, MD, PhD, FACC
New York, New York

This review summarizes important advances in atherothrombosis within the last year, with a particular emphasis on risk factors and markers of disease, progress in imaging, and advances in therapy. Major journals in cardiology and internal medicine published in English and in PubMed were carefully searched for relevant studies in all 3 categories. Representative articles were selected on the basis of clinical relevance and scientific merit.

Markers of Cardiovascular Risk and/or Disease

Traditional risk factors. Early detection and risk stratification continued to be some of the main focuses of atherothrombosis research. In parallel with the quest for novel disease markers, the substantial impact of conventional risk factors was emphasized in several reports. Cardiovascular disease has become the global leading cause of death worldwide (Fig. 1). Furthermore, arterial hypertension, hypercholesterolemia, and smoking lead the list of risk factors associated with mortality (1). A large international registry showed that the risk profile in atherothrombotic patients is similar throughout the world, although risk factors are largely undertreated and undercontrolled (2). The growing impact of obesity as an independent risk factor received particular attention. Large, prospective studies showed that not only obesity but also excess weight is independently associated with increased mortality in both men and women, and across various age and ethnic groups (3). Emphasizing the difference between adipose and lean mass, the waist-to-hip ratio was a stronger independent marker of risk of myocardial infarction than the body mass index in a study of 27,000 patients worldwide (4). There was also increasing evidence of the importance of air pollution at common levels of exposure as a novel risk factor, associated with increased vascular inflammation and atherogenesis in apolipoprotein E knockout mice (5).

Physical markers. An abnormally low (<1.1) or high (>1.4) ankle-brachial index as an indicator of peripheral disease was shown to predict increased future cardiovascular events in the general population after adjustment for potential confounders (6). In addition, prospective evidence accumulated regarding the prognostic significance of measurements of arterial stiffness, specifically aortic pulse wave velocity (7).

Serum biomarkers. The importance of the link between inflammation and atherothrombosis was reiterated by the largest published series so far evaluating histologic features of symptomatic carotid plaques, in which inflammation showed the strongest association with plaque instability (8). The role and implications of C-reactive protein (CRP) continued to be a major focus of attention. Data from the Dallas Heart Study showed no association of CRP concentrations with the burden of subclinical atherosclerosis, suggesting that they reflect different aspects of the disease (9). To understand the sources of serum CRP level variability, a substudy of the Framingham offspring cohort reported that 12 clinical variables (that spanned conventional markers of risk) explained 26% of CRP concentration variability (the body mass index alone explained 15%). In addition, a single-nucleotide polymorphism with independent association with CRP levels was identified, although it explained only 1.4% of total variability (10). Whether CRP represents a bystander or a contributor to disease progression continued to be a matter of debate. Newly described potentially proatherogenic actions of CRP included induction of matrix metalloproteinases-1 and -10 secretion (11), and the activation of nuclear factor κB, a central mediator in atherogenesis (12). However, a study in >3,000 women evaluating the distribution of CRP haplotypes and metabolic syndrome phenotype did not suggest a causal role of CRP within this clinical context (13).

Another serum biomarker that gained significant attention was adiponectin, an adipocyte-derived peptide with anti-inflammatory and antiatherogenic properties. Although decreased serum concentrations have been advocated as a strong predictor of incident coronary heart disease, a large prospective study with a concomitant meta-analysis of prior prospective investigations showed a modest, nonsignificant association (14). Regarding hemostatic markers, elevated levels of fibrinogen, plasminogen activator inhibitor-1, and D-dimer were independently associated with increased incidence of cardiovascular events, whereas factor VIIc showed an inverse association (15). The interaction between inflammation and coagulability was evaluated measuring platelet gene expression of myeloid-related protein 14, a chemoattractant that regulates leukocyte ad-

From The Zena and Michael A. Wiener Cardiovascular Institute/Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, New York.
Manuscript received November 10, 2006; accepted November 21, 2006.

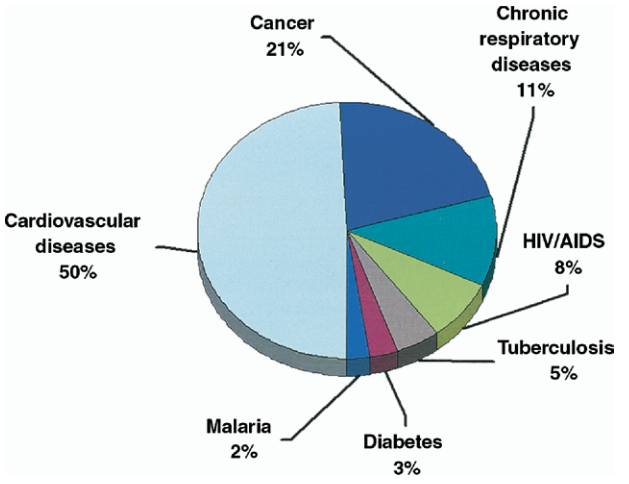

Figure 1 **Worldwide Causes of Death Secondary to Chronic Diseases**

Reprinted with permission from Fuster V, Voute J. MDGs: chronic diseases are not on the agenda. Lancet 2005;366:1512–14. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

hesion. In comparison with subjects with stable disease, patients with acute myocardial infarction showed higher plasmatic concentrations of myeloid-related protein 14. Most importantly, serum levels prospectively predicted cardiovascular events above and beyond CRP and conventional risk factors (16).

Substantial evidence accumulated on the ability of brain natriuretic peptide (BNP) to predict future cardiovascular events in several patient subgroups. Results from the Atherogene Study confirmed markedly increased cardiovascular risk in patients with stable angina and elevated plasma BNP levels after adjustment for conventional risk factors, CRP, multivessel disease, and left ventricular ejection fraction (17). In addition, persistent BNP elevation may identify those individuals remaining at higher risk after an acute event (18). Troponin I was shown to predict mortality and incident coronary disease in older men after adjusting for conventional risk factors, suggesting that subclinical cardiac damage strongly influences prognosis (19). A substudy of the OPUS–TIMI (Orbofiban in Patients with Unstable Coronary Syndromes–Thrombolysis In Myocardial Infarction) 16 trial evaluated the prognostic significance of heart-type fatty acid binding protein, another protein released from the myocardium in response to injury. During a 10-month follow-up after an acute coronary syndrome, subjects with elevated concentrations were more likely to suffer death, myocardial infarction, or congestive heart failure, even after accounting for clinical variables, troponin I, or BNP (Fig. 2) (20).

Clinical implications of serum biomarkers versus traditional risk factors. The practical value of measuring individual biomarkers was questioned in a report from the ARIC (Atherosclerosis Risk in Communities) study, in which 19 novel markers of inflammation, thrombogenicity, oxidative stress, endothelial function, or chronic infection were quantified in 15,792 individuals. The ability to predict the 5-year incidence of coronary disease by conventional risk factors was insignificantly or only marginally improved by novel biomarkers, including CRP (21). Similar results were communicated in the setting of secondary prevention in a subset of 3,199 patients enrolled in the HOPE (Heart Outcomes Prevention Evaluation) study. In another multivariate model that included conventional prognosticators, several biomarkers (N-terminal pro-BNP, soluble intercellular adhesion molecule 1, microalbuminuria, soluble interleukin-1 receptor antagonist, and fibrinogen) remained significantly associated with the risk of infarction, stroke, or cardiovascular death. However, only the addition of N-terminal pro-BNP provided incremental predictive accuracy to the model, even when combinations of multiple biomarkers were evaluated (22). Although these results do not necessarily invalidate the quantification of serum markers for the prediction of specific outcomes or in selected patient subsets, they again emphasized the importance of conventional, modifiable risk factors.

Endothelial repair and progenitor cells. Endothelial progenitor cells (EPCs) derive from different organs (predominantly the bone marrow) and play an important role in endogenous repair of endothelium damaged by risk factors or other mechanisms. Low plasmatic levels of CD34+ EPCs were associated with various cardiovascular risk factors (including the metabolic syndrome) and were independent predictors of high Framingham risk scores (23). Some studies found an inverse correlation between EPC levels and atherosclerosis extent (24). These results suggest that continued vascular damage associated with insufficient reparative ability might result in increased atherosclerosis. Nonetheless, one study paradoxically reported an independent association between elevated EPC number and angio-

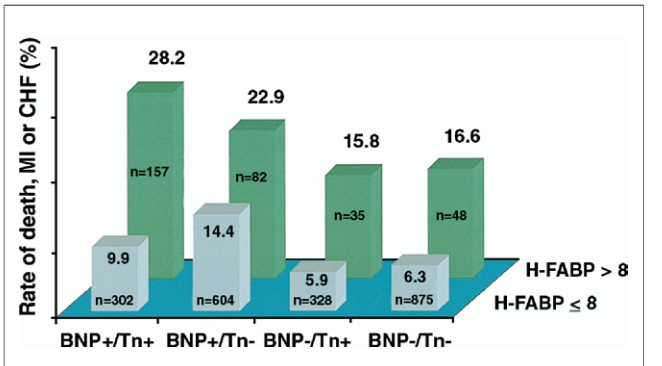

Figure 2 **Predictive Value of H-FABP After an Acute Coronary Syndrome**

Rates of death, myocardial infarction (MI), or congestive heart failure (CHF) stratified by baseline concentration of brain natriuretic peptide (BNP), troponin I (Tn), or heart-type fatty acid binding protein (H-FABP) in the OPUS-TIMI 16 study. BNP + = BNP >80 pg/ml; Tn + = troponin I >1.5 ng/ml. Reproduced with permission from O'Donoghue et al. (20).

graphic coronary disease severity, with the highest numbers obtained in patients requiring revascularization (25). Hence, our understanding of the interaction between EPC levels and disease state is still evolving and requires additional research. This controversy was elegantly discussed by Leor and Marber (26), highlighting the potential shortcomings of attempting clinical studies before understanding the pathophysiological role of endogenous EPCs.

Genetic markers. Novel genetic polymorphisms associated with increased risk included a variant of the vitamin K epoxide reductase gene, involved in the synthesis of coagulation factors, or endothelial nitric oxide synthase, required for the generation of the protective molecule nitric oxide (27,28). Nonetheless, the difficulty of identifying clinically meaningful genetic polymorphisms was highlighted in a large meta-analysis of 191 studies (n >150,000) studying 7 hemostatic genes. Only 2 variants of the factor V and prothrombin genes showed significant, although weak, associations with coronary disease (29). Another polymorphism of growing interest is related to the haptoglobin protein, a defensive mechanism responsible for antagonizing the deleterious effects of extracorpuscular hemoglobin during episodes of intraplaque hemorrhage (30). Two common alleles exist at the haptoglobin locus (1 and 2), and the haptoglobin-2 allele is associated with decreased antioxidative and anti-inflammatory activity of haptoglobin, resulting in increased vascular damage. These effects were demonstrated in vivo, showing increased iron deposition, lipid peroxidation, and macrophage accumulation in atherosclerotic plaques from apolipoprotein E knockout haptoglobin-2 transgenic mice (31) (Fig. 3).

Imaging of Atherothrombosis

Invasive techniques. Intravascular ultrasound (IVUS) consolidated during 2006 as a powerful tool for the evaluation of coronary atherosclerotic burden, which cannot be reliably predicted by luminal angiography or assessment of cardiovascular risk factors alone (32). Serial IVUS evaluations showed that progression of disease is associated with eccentric remodeling that is not limited by plaque extent, whereas plaque stabilization and regression are accompanied by constrictive remodeling (33). A study evaluating the 3 main coronary arteries with IVUS and radiofrequency data analysis (virtual histology) in patients referred for intervention showed that patients with at least 1 plaque rupture presented a larger plaque burden despite a similar lumen cross-sectional area (34). In addition, as discussed in the section Therapy, IVUS studies provided important mechanistic insights of the beneficial effects of antiatherosclerotic treatments (Fig. 4).

Intracoronary angioscopy was evaluated as a potential tool for prognostic stratification. In a prospective evaluation including >500 patients, the presence and number of yellow

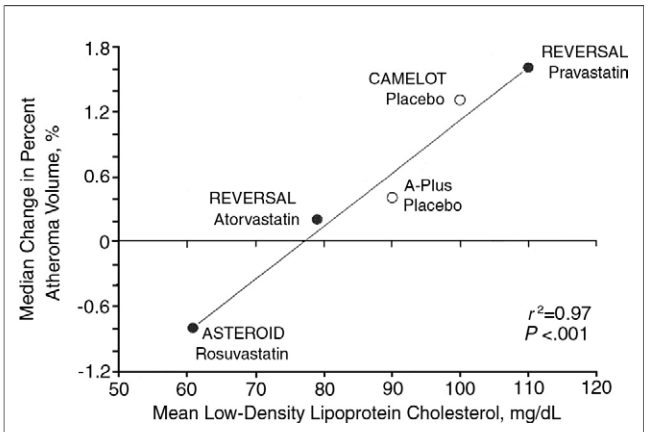

Figure 4 LDL Cholesterol and Coronary Disease Progression

Relationship between plasmatic low-density lipoprotein (LDL) cholesterol levels and progression/regression of disease (quantified as median change in percent atheroma volume) as derived from several intravascular ultrasound trials. Reproduced from Nissen et al. (65). (JAMA, April 5, 2006, Vol. 295, page 1563; Copyright © [2006], *American Medical Association*. All rights reserved.)

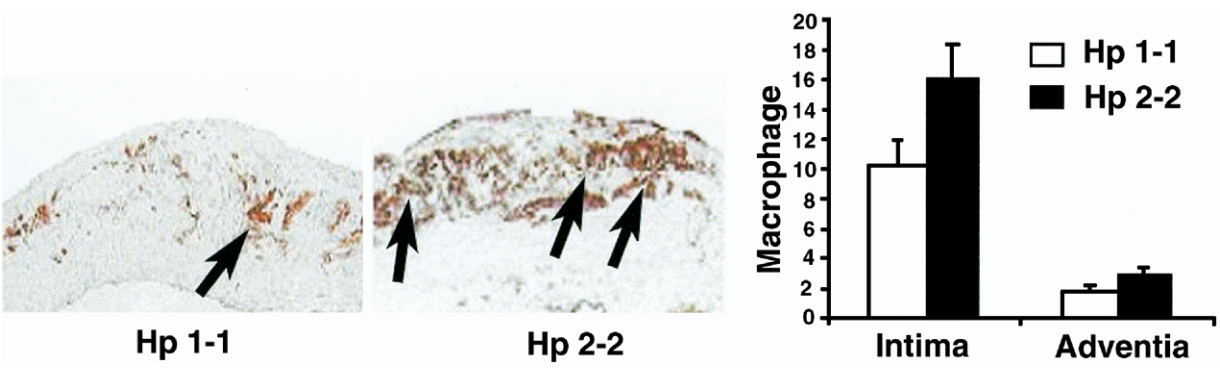

Figure 3 Plaque Inflammation and Haptoglobin Variants

Color illustrations and bar graphs comparing macrophage content in atherosclerotic plaques of apolipoprotein E knockout mice with the haptoglobin (Hp) 1-1 or Hp 2-2 genotype. Increased macrophage infiltration **(black arrows)** is noted in the Hp 2-2 plaques. Adapted with permission from Levy et al. (31).

plaques (a feature suggestive of large lipid cores and thin fibrous caps) was independently associated with future risk of acute coronary syndromes (35).

Computed tomography. New reference values of coronary calcium distribution in subjects without clinical cardiovascular disease (or treated diabetes) became available from the MESA (Multi-Ethnic Study of Atherosclerosis) trial, allowing for improved interpretation of the degree of coronary calcification according not only to age and gender, but also to ethnicity (36). Data from the same cohort suggested that the prevalence of hyperlipidemia requiring drug therapy is ~30%; however, in approximately 45% of the remaining subjects there was detectable coronary calcification, and in 7% the score was >400, indicative of high cardiovascular risk (37). Similar observations prompted a provocative expert consensus statement proposing a new paradigm in primary prevention, guided by universal noninvasive atherosclerosis imaging (specifically carotid intima-media thickness and coronary calcium scoring) in all asymptomatic intermediate-risk subjects as defined by age and gender (38).

Garcia et al. (39) reported the first multicenter comparison of 16-slice multidetector computed tomography (MDCT) and invasive coronary angiography in 187 patients, using quantitative determination of stenosis degree. After including all nonevaluable segments (29%) in the analysis as positive, the per-patient sensitivity, specificity, positive predictive value, and negative predictive value for the detection of >50% luminal diameter narrowing were 98%, 54%, 50%, and 99%, respectively. Subsequently, a meta-analysis of 29 studies (>2,000 patients) comparing ≥16-slice MDCT and invasive angiography reported pooled values of 96%, 74%, 83%, and 94% for the same parameters. These results were reached after exclusion from the analysis of 4.2% unassessable segments, and inclusion of 6.4% nonevaluable segments categorized at the discretion of the investigators. A trend was noted for a small improvement in accuracy for 64-slice scanners. These results underscore a moderate specificity and a high negative predictive value, with a potential role in patients with low to intermediate disease prevalence (40).

Cardiac magnetic resonance. Another meta-analysis of 50 studies of coronary angiography with MDCT (4- and 16-slice) or magnetic resonance imaging (MRI) showed superior performance of MDCT at the present time (Fig. 5) (41). Additional relevant information that can be obtained with MRI includes delayed enhancement. To evaluate the prognostic implications of subclinical myocardial damage, the presence of newly found myocardial scarring was the strongest predictor of cardiac events and mortality in one study, even after adjusting for risk factors, coronary anatomy, ejection fraction, or wall motion abnormalities (42). Moreover, the extent of MRI-determined peri-infarct zone was identified as a novel independent predictor of cardiovascular mortality (43). In addition, a MESA substudy showed negative correlations between atherosclerosis extent and both regional systolic and diastolic function using MRI tagging, suggesting an early negative impact of subclinical atherosclerosis before overt myocardial failure (44).

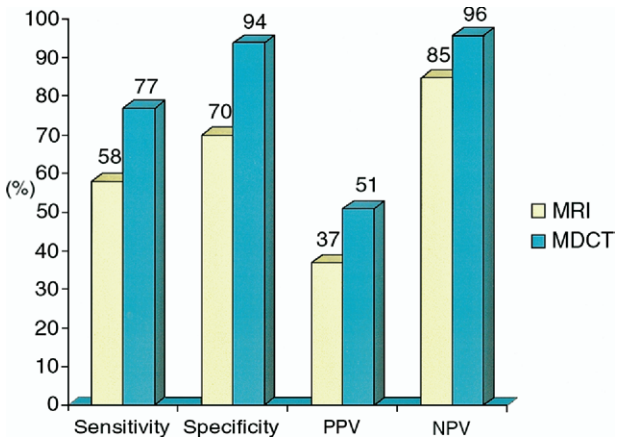

Figure 5 **Diagnostic Performance of Coronary Angiography With MRI and MDCT**

Weighted sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of coronary angiography with multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) after inclusion of unassessable segments. Data from Schuijf et al. (41).

Noninvasive visualization of the vessel wall. Data from the Dallas Heart Study showed that quantification of aortic plaque burden with MRI detected subclinical atherosclerosis more often than calcium scoring (9). Another investigation described an association of complex plaques in the abdominal aorta and the coronary tree, consistent with systemic atherosclerosis instability (45). Multicontrast, high-resolution MRI was used in a prospective evaluation in 154 patients with asymptomatic 50% to 79% carotid stenosis. Several plaque features (intraplaque hemorrhage, large necrotic core, maximum wall thickness, and particularly a thin or ruptured fibrous cap) were identified as strong predictors of subsequent ipsilateral cerebrovascular events (46). In addition, measurements derived from kinetic modeling of the first pass of contrast through carotid plaques showed strong correlations with macrophage content and neovascularization degree, supporting a possible role for the detection of inflammatory activity and vulnerability (47). Underscoring the importance of merging different imaging modalities, Davies et al. (48) combined MRI for plaque visualization and ^{18}fluorodeoxyglucose positron emission tomography for the detection of inflammatory activity, and suggested a potential use in the identification of culprit lesions (Fig. 6).

Molecular imaging. Through the visualization of specific molecular processes with known roles in atherosclerosis development and progression, molecular imaging continued to develop as a tool for the evaluation of disease activity. Novel imaging probes were able to detect expression of vascular adhesion molecule-1 or the action of matrix metalloproteinases in vivo (49,50). Moreover, the possibil-

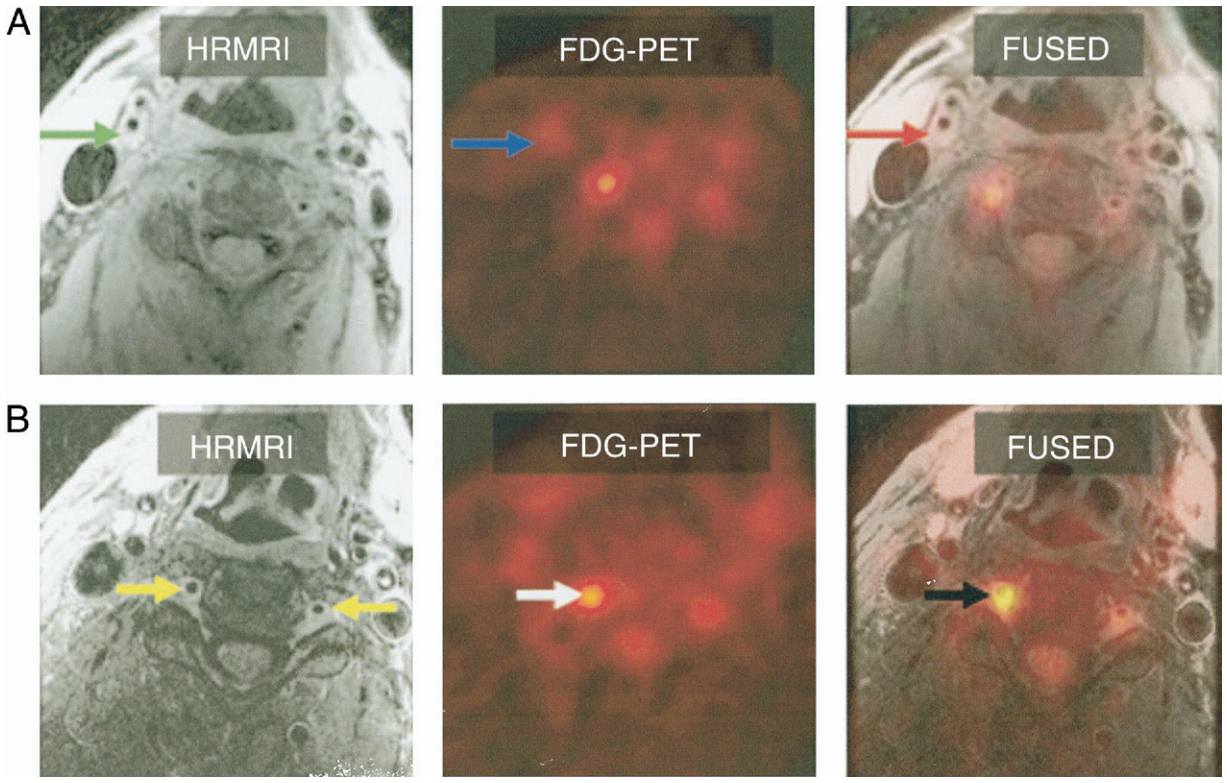

Figure 6 **Combined PET and MRI Detection of Plaque Inflammation**

Transaxial cervical images obtained with high-resolution magnetic resonance imaging (HRMRI), ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET), and fused images (FUSED) in a patient with transient right visual disturbance. **(Row A)** The magnetic resonance imaging (MRI) shows a large stenotic plaque in the right internal carotid artery **(green arrow)**, which only shows mild radiotracer uptake on the FDG-PET and fused images **(blue and red arrows)**. **(Row B)** At a different position, MRI shows the vertebral arteries **(yellow arrows)**, whereas the FDG-PET and fused images show a highly inflamed right vertebral artery plaque **(white and black arrows)** that could be the cause of the patient's symptoms. Reproduced with permission from Davies et al. (48).

ity of using synthetic high-affinity molecular agents as carriers for therapeutic agents was also explored. The role of plaque neovascularization in atherogenesis and vulnerability was reviewed in detail in 2006 (51), and a nanoparticle targeted to $\alpha_v\beta_3$ integrins was coupled with fumagillin, an antiangiogenic agent, in an attempt to decrease plaque neovasculature in an experimental model of atherosclerosis. The drug successfully reduced the amount of neovessels (as confirmed by histology), and these actions could be tracked in vivo with MRI (52).

Therapy

Risk factor management. Several trials evaluated the effects of lifestyle changes on cardiovascular risk. In a large cohort of postmenopausal women, a low-fat diet had modest effects on cardiovascular risk factors and failed to decrease events after an 8-year follow-up (53). On the other hand, a smaller trial in high-risk patients that compared a low-fat diet with a Mediterranean diet showed significantly larger reductions in risk factors with the latter (54). Aside from the well-known benefits of exercise, high levels of energy expenditure during daily activities were prospectively associated with increased survival in a cohort of older adults (55). Another study in a large prospective cohort of 40- to 75-year-old men free of disease (n = 42,847) estimated that >60% of primary coronary events could be prevented by adoption of a healthy lifestyle (defined as regular exercise, absence of smoking, controlled weight, moderate alcohol consumption, and a healthy diet) (56). Several trials evaluated the efficacy of varenicline, a novel partial agonist of the $\alpha4\beta2$ nicotinic acetylcholine receptor, for smoking cessation. After a 12-week period of therapy, the rates in continuous smoking absence at 1 year were significantly higher for varenicline (23%) than with bupropion (14.6%) or placebo (10.3%) (57). The cannabinoid-1 receptor blocker antagonist rimonabant for weight loss in obese and overweight patients caused significant weight loss and favorable effects in cardiometabolic risk factors in the RIO–NA (Rimonabant In Obesity–North America) trial. Nonetheless, these benefits were lost after interruption of the drug (58).

Updated guidelines for secondary prevention of atherothrombotic events were released in 2006 (59). However, lack of compliance with prescribed therapy remains a widespread problem. In this regard, a study suggested cost-

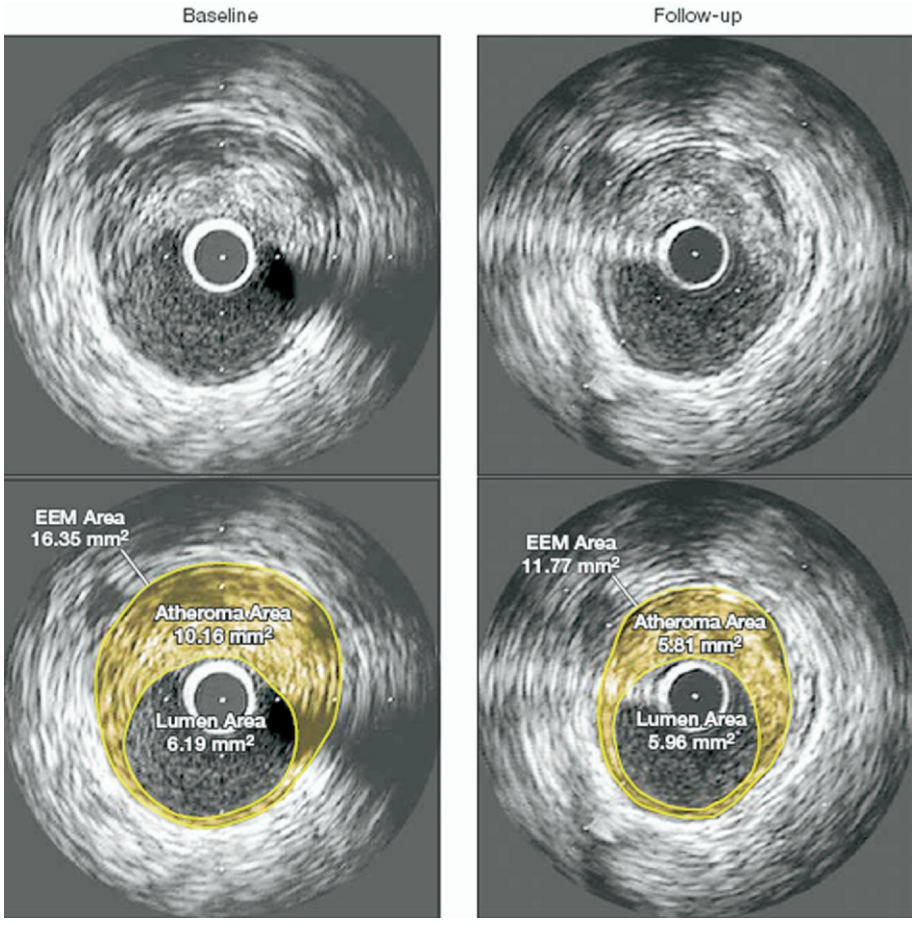

Figure 7 **Coronary Atheroma Regression Associated With High-Intensity Statin Therapy**

(Top) Baseline and follow-up intravascular ultrasound images of a single coronary cross section after 24 months of rosuvastatin treatment. **(Bottom)** Measurements superimposed on the same cross sections, showing the reduction in atheroma area. EEM = external elastic membrane. Reproduced with permission from Nissen et al. (65). (JAMA, April 5, 2006, Vol. 295, page 1563; Copyright © [2006], *American Medical Association.* All rights reserved.)

effectiveness of fixed combinations of drugs in 1 single pill (polypill) both in primary and in secondary prevention (60).

Some studies evaluated therapy targeted to novel cardiac risk factors. Despite prior evidence of an independent relation between homocysteine and cardiovascular disease, large randomized placebo-controlled trials failed to show benefits of homocysteine lowering with folic acid and vitamin B_6/B_{12} supplements, and in fact suggested a trend for a detrimental effect (61).

Lipid therapy. Several studies addressed the protective effects of high-intensity statin treatment. Meta-analyses of 4 studies (n = 27,548) of stable disease (TNT [Treating to New Targets] and IDEAL [Incremental Decrease in End Points Through Aggressive Lipid Lowering]) or acute coronary syndromes (A-to-Z [Aggrastat to Zocor] and PROVE IT–TIMI-22 [PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction]) showed a significant decrease not only in the incidence of coronary death or myocardial infarction (62), but also in development of heart failure, independent of recurrent infarct (63). Similarly, intensive statin therapy early after an acute coronary syndrome was associated with clinical benefits that became evident after 4 to 12 months (64). In the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial (65), aggressive therapy with rosuvastatin 40 mg/day led to an average 53% low-density lipoprotein (LDL) cholesterol reduction, 15% high-density lipoprotein (HDL) cholesterol increase, and absolute regression of atheroma volume as shown by IVUS (Fig. 7). Finally, the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) Trial tested atorvastatin 80 mg/day in 4,731 patients with a recent stroke or transitory ischemic attack, LDL = 100 to 190 mg/dl, and no known coronary disease. After a median of 5 years, atorvastatin was associated not only with a 16% relative risk reduction for recurrent stroke (11.2% vs. 13.1%, p = 0.03) in comparison with

Table 1 Summary of Outcomes in the CHARISMA Trial

	Aspirin + Clopidogrel (n = 7,802)	Aspirin + Placebo (n = 7,801)	Relative Risk (95% Confidence Intervals)	p Value
Primary efficacy end point	6.8%	7.3%	0.93 (0.83–1.05)	0.22
Principal secondary efficacy end point	16.7%	17.9%	0.92 (0.86–0.99)	0.04
Nonfatal stroke	1.9%	2.4%	0.79 (0.64–0.98)	0.03
Hospitalization	11.1%	12.3%	0.90 (0.82–0.98)	0.02
Severe bleeding	1.7%	1.3%	1.25 (0.97–1.61)	0.09
Moderate bleeding	2.1%	1.3%	1.62 (1.27–2.08)	<0.001

The primary efficacy end point includes cardiovascular death, myocardial infarction, and stroke. The secondary efficacy end point includes the same events plus hospitalization (because of unstable angina, transient ischemic attack or revascularization). Individual end points with statistically significant difference between the groups are also shown. Data from Bhatt et al. (79).
CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance.

placebo, but also with a decrease in the rate of coronary events (66).

Another relevant aspect of lipid therapy was HDL. A post hoc analysis of the BIP (Bezafibrate Infarction Prevention) trial suggested that the degree of HDL elevation obtained with bezafibrate, a peroxisome proliferator-activated receptor (PPAR)-α agonist, was independently associated with reduced cardiac mortality (67). In addition, a study evaluating the effects of fenofibrate on experimental atherosclerosis with MRI showed a 36% increase in plasma HDL concentration and plaque regression (68). These favorable effects may be attributable not only to HDL augmentation but also to other antiatherogenic properties of PPAR agonists (see subsequent text). As a novel antiatherogenic mechanism, HDL was shown to enhance EPC recruitment into damaged endothelium (69). Despite these potential benefits of augmenting HDL levels, a phase III clinical trial using the cholesterylester transfer protein inhibitor torcetrapib was prematurely stopped due to increased mortality in the torcetrapib-atorvastatin arm in comparison with atorvastatin alone (70). Alternative HDL-raising therapies in development include liver X receptor agonists, recently proven to enhance reverse cholesterol transport (71), and oral HDL mimetic peptides (72).

Other tested therapies included pactimibe, a potentially antiatherogenic acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitor that could enhance reverse cholesterol transport. In the ACTIVATE (ACAT Intravascular Atherosclerosis Treatment Evaluation) trial (73), pactimibe failed to reduce total IVUS-determined coronary atheroma volume and seemed to be actually proatherogenic. Also, a preliminary dose-escalation study in healthy volunteers testing an antisense oligonucleotide with the ability to inhibit apolipoprotein B synthesis reported 35% reductions in LDL cholesterol (74).

Antithrombotic therapy. There was increasing concern regarding the not uncommon resistance to antiplatelet agents. A potential contributor to aspirin resistance is residual arachidonic acid activity, through a cyclooxygenase (COX)-independent mechanism, causing platelet activation despite treatment with aspirin (75). In the case of clopidogrel resistance, prasugrel, a more potent thienopyridine, may be a promising alternative according to preliminary studies (76). Regarding the deleterious effects of COX-2 inhibition, initial experimental evidence suggested that some may be counteracted by low-dose clopidogrel (77). In addition, increased cardiovascular risk was shown not only with selective COX-2 inhibitors but also with frequent use of nonselective nonsteroidal anti-inflammatory drugs, including acetaminophen (78). These findings likely reflect the complex influence on atherosclerosis of COX-1 and -2 balanced activities.

The highlight of the year in terms of antithrombotic therapy came from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, which randomized 15,603 symptomatic (defined as documented coronary, cerebrovascular, or peripheral arterial disease) and asymptomatic patients with multiple risk factors (a significant percentage of whom had prior cardiovascular events) to aspirin plus clopidogrel or aspirin plus placebo. There were no significant differences in the rate of the primary composite outcome, with a marginally significant benefit for the clopidogrel group in the principal secondary end point, at the cost of increased risk of moderate bleeding (Table 1). Importantly, although there was suggestion of a benefit with clopidogrel in the primary outcome for symptomatic patients (6.9% vs. 7.9%, p = 0.046), the rate of cardiovascular death was higher in the asymptomatic group receiving clopidogrel (3.9% vs. 2.2%, p = 0.01) (79). Concordant effects of dual antiaggregation were reported in the ESPRIT (Estrogen in the Prevention of Reinfarction Trial), which randomized patients with minor ischemic stroke or transitory ischemic attack in the past 6 months to aspirin alone or aspirin plus dipyridamole. The results of the trial and those of a meta-analysis of prior studies published simultaneously showed a significant reduction of the combination of vascular death, infarction, or recurrent stroke (80). Finally, novel approaches for antiplatelet therapy included dual antagonism of platelet receptors for thrombin (81), or oral, reversible adenosine diphosphate receptor blockers that, unlike thienopyridines, do not require metabolic activation (82).

Additional therapies. A meta-analysis of 3 large trials (HOPE, PEACE [Prevention of Events With Angiotensin-Converting Enzyme Inhibition], and EUROPA [European Trial on Reduction of Cardiac Events With Perindopril in

Stable Coronary Artery Disease]) evaluating the effects of angiotensin-converting enzyme inhibitors in patients with established atherosclerosis but without heart failure or left ventricular dysfunction reported an 18% relative risk decrease in the incidence of cardiovascular death, infarction, or stroke (83).

Finally, important information regarding the management of diabetic atherosclerosis became available in the last year. In the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) trial, 5,238 patients with type 2 diabetes and evidence of macrovascular disease were prospectively randomized to pioglitazone (a PPAR-γ activator) or placebo. After an average follow-up of 34 months, pioglitazone was associated with a significant reduction in the composite end point of death, nonfatal myocardial infarction, and stroke (hazard ratio 0.84, p = 0.027) (84). Moreover, novel applications of thiazolidinediones in nondiabetic patients are being explored, and pioglitazone was shown to increase HDL, improve endothelial function, and reduce inflammatory markers (85).

Reprint requests and correspondence: Dr. Valentin Fuster, Cardiovascular Institute, Mount Sinai Hospital, One Gustave L. Levy Place, Box 1030, New York, New York 10029. E-mail: valentin.fuster@mssm.edu.

REFERENCES

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747–57.
2. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180–9.
3. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;355:763–78.
4. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005;366:1640–9.
5. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA 2005;294:3003–10.
6. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006;113:388–93.
7. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113:657–63.
8. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. Circulation 2006;113:2320–8.
9. Khera A, de Lemos JA, Peshock RM, et al. Relationship between C-reactive protein and subclinical atherosclerosis: the Dallas Heart Study. Circulation 2006;113:38–43.
10. Kathiresan S, Larson MG, Vasan RS, et al. Contribution of clinical correlates and 13 C-reactive protein gene polymorphisms to interindividual variability in serum C-reactive protein level. Circulation 2006;113:1415–23.
11. Montero I, Orbe J, Varo N, et al. C-reactive protein induces matrix metalloproteinase-1 and -10 in human endothelial cells: implications for clinical and subclinical atherosclerosis. J Am Coll Cardiol 2006;47:1369–78.
12. Liang Y-J, Shyu K-G, Wang B-W, Lai L-P. C-reactive protein activates the nuclear factor-κB pathway and induces vascular cell adhesion molecule-1 expression through CD32 in human umbilical vein endothelial cells and aortic endothelial cells. J Mol Cell Cardiol 2006;40:412–20.
13. Timpson NJ, Lawlor DA, Harbord RM, et al. C-reactive protein and its role in metabolic syndrome: mendelian randomisation study. Lancet 2005;366:1954–9.
14. Sattar N, Wannamethee G, Sarwar N, et al. Adiponectin and coronary heart disease: a prospective study and meta-analysis. Circulation 2006;114:623–9.
15. Smith A, Patterson C, Yarnell J, Rumley A, Ben-Shlomo Y, Lowe G. Which hemostatic markers add to the predictive value of conventional risk factors for coronary heart disease and ischemic stroke? The Caerphilly Study. Circulation 2005;112:3080–7.
16. Healy AM, Pickard MD, Pradhan AD, et al. Platelet expression profiling and clinical validation of myeloid-related protein-14 as a novel determinant of cardiovascular events. Circulation 2006;113:2278–84.
17. Schnabel R, Lubos E, Rupprecht HJ, et al. B-type natriuretic peptide and the risk of cardiovascular events and death in patients with stable angina: results from the AtheroGene study. J Am Coll Cardiol 2006;47:552–8.
18. Morrow DA, de Lemos JA, Blazing MA, et al. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. JAMA 2005;294:2866–71.
19. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. Circulation 2006;113:1071–8.
20. O'Donoghue M, de Lemos JA, Morrow DA, et al. Prognostic utility of heart-type fatty acid binding protein in patients with acute coronary syndromes. Circulation 2006;114:550–7.
21. Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. Arch Intern Med 2006;166:1368–73.
22. Blankenberg S, McQueen MJ, Smieja M, et al. Comparative impact of multiple biomarkers and N-terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. Circulation 2006;114:201–8.
23. Fadini GP, de Kreutzenberg SV, Coracina A, et al. Circulating CD34+ cells, metabolic syndrome, and cardiovascular risk. Eur Heart J 2006;27:2247–55.
24. Kunz GA, Liang G, Cuculoski F, et al. Circulating endothelial progenitor cells predict coronary artery disease severity. Am Heart J 2006;152:190–5.
25. Güven H, Shepherd RM, Bach RG, Capoccia BJ, Link DC. The number of endothelial progenitor cell colonies in the blood is increased in patients with angiographically significant coronary artery disease. J Am Coll Cardiol 2006;48:1579–87.
26. Leor J, Marber M. Endothelial progenitors: a new Tower of Babel? J Am Coll Cardiol 2006;48:1588–90.
27. Wang Y, Zhang W, Zhang Y, et al. VKORC1 haplotypes are associated with arterial vascular diseases (stroke, coronary heart disease, and aortic dissection). Circulation 2006;113:1615–21.
28. Rossi GP, Maiolino G, Zanchetta M, et al. The T(-786)C endothelial nitric oxide synthase genotype predicts cardiovascular mortality in high-risk patients. J Am Coll Cardiol 2006;48:1166–74.
29. Ye Z, Liu EH, Higgins JP, et al. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66,155 cases and 91,307 controls. Lancet 2006;367:651–8.
30. Levy AP, Moreno PR. Intraplaque hemorrhage. Curr Mol Med 2006;6:479–88.
31. Levy AP, Levy JE, Kalet-Litman S, et al. Haptoglobin genotype is a determinant of iron, lipid peroxidation, and macrophage accumulation in the atherosclerotic plaque. Arterioscler Thromb Vasc Biol 2007;27:134–40.
32. Nicholls SJ, Tuzcu EM, Crowe T, et al. Relationship between cardiovascular risk factors and atherosclerotic disease burden measured by intravascular ultrasound. J Am Coll Cardiol 2006;47:1967–75.
33. Schoenhagen P, Tuzcu EM, Apperson-Hansen C, et al. Determinants of arterial wall remodeling during lipid-lowering therapy: serial intravascular ultrasound observations from the Reversal of Atherosclerosis

with Aggressive Lipid Lowering Therapy (REVERSAL) trial. Circulation 2006;113:2826–34.
34. Rodriguez-Granillo GA, Garcia-Garcia HM, Valgimigli M, et al. Global characterization of coronary plaque rupture phenotype using three-vessel intravascular ultrasound radiofrequency data analysis. Eur Heart J 2006;27:1921–7.
35. Ohtani T, Ueda Y, Mizote I, et al. Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angioscopy. J Am Coll Cardiol 2006;47:2194–200.
36. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2006;113:30–7.
37. Goff DC Jr., Bertoni AG, Kramer H, et al. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. Circulation 2006;113:647–56.
38. Naghavi M, Falk E, Hecht HS, et al. From vulnerable plaque to vulnerable patient—part III: executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol 2006;98:2H–15H.
39. Garcia MJ, Lessick J, Hoffmann MH. Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis. JAMA 2006;296:403–11.
40. Hamon M, Biondi-Zoccai GGL, Malagutt P, et al. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. J Am Coll Cardiol 2006;48:1896–910.
41. Schuijf JD, Bax JJ, Shaw LJ, et al. Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography. Am Heart J 2006;151:404–11.
42. Kwong RY, Chan AK, Brown KA, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation 2006;113:2733–43.
43. Yan AT, Shayne AJ, Brown KA, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. Circulation 2006;114:32–9.
44. Fernandes VR, Polak JF, Edvardsen T, et al. Subclinical atherosclerosis and incipient regional myocardial dysfunction in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol 2006;47:2420–8.
45. Momiyama Y, Kato R, Fayad ZA, et al. A possible association between coronary plaque instability and complex plaques in abdominal aorta. Arterioscler Thromb Vasc Biol 2006;26:903–9.
46. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI—initial results. Stroke 2006;37:818–23.
47. Kerwin WS, O'Brien KD, Ferguson MS, Polissar N, Hatsukami TS, Yuan C. Inflammation in carotid atherosclerotic plaque: a dynamic contrast-enhanced MR imaging study. Radiology 2006;241:459–68.
48. Davies JR, Rudd JHF, Fryer TD, et al. Identification of culprit lesions after transient ischemic attack by combined 18F fluorodeoxyglucose positron-emission tomography and high-resolution magnetic resonance imaging. Stroke 2005;36:2642–7.
49. Nahrendorf M, Jaffer FA, Kelly KA, et al. Noninvasive vascular cell adhesion molecule-1 imaging identifies inflammatory activation of cells in atherosclerosis. Circulation 2006;114:1504–11.
50. Deguchi JO, Aikawa M, Tung CH, et al. Inflammation in atherosclerosis: visualizing matrix metalloproteinase action in macrophages in vivo. Circulation 2006;114:55–62.
51. Moreno PR, Purushothaman KR, Sirol M, Levy AP, Fuster V. Neovascularization in human atherosclerosis. Circulation 2006;113:2245–52.
52. Winter PM, Neubauer AM, Caruthers SD, et al. Endothelial alpha(v)beta3 integrin-targeted fumagillin nanoparticles inhibit angiogenesis in atherosclerosis. Arterioscler Thromb Vasc Biol 2006;26:2103–9.
53. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:655–66.
54. Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 2006;145:1–11.
55. Manini TM, Everhart JE, Patel KV, et al. Daily activity energy expenditure and mortality among older adults. JAMA 2006;296:171–9.
56. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. Circulation 2006;114:160–7.
57. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296:56–63.
58. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006;295:761–75.
59. Smith SC Jr., Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol 2006;47:2130–9.
60. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. Lancet 2006;368:679–86.
61. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578–88.
62. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006;48:438–45.
63. Scirica BM, Morrow DA, Cannon CP, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol 2006;47:2326–31.
64. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:1814–21.
65. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556–65.
66. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–59.
67. Goldenberg I, Goldbourt U, Boyko V, Behar S, Reicher-Reiss H. Relation between on-treatment increments in serum high-density lipoprotein cholesterol levels and cardiac mortality in patients with coronary heart disease (from the Bezafibrate Infarction Prevention Trial). Am J Cardiol 2006;97:466–71.
68. Corti R, Osende J, Hutter R, et al. Fenofibrate induces plaque regression in hypercholesterolemic atherosclerotic rabbits: in vivo demonstration by high-resolution MRI. Atherosclerosis 2007;190:106–13.
69. Tso C, Martinic G, Fan WH, Rogers C, Rye KA, Barter PJ. High-density lipoproteins enhance progenitor-mediated endothelium repair in mice. Arterioscler Thromb Vasc Biol 2006;26:1144–9.
70. Tall AR, Yvan-Charvet L, Wang N. The failure of torcetrapib. Was it the molecule or the mechanism? Arterioscler Thromb Vasc Biol 2007;27:257–60.
71. Naik SU, Wang X, Da Silva JS, et al. Pharmacological activation of liver X receptors promotes reverse cholesterol transport in vivo. Circulation 2006;113:90–7.
72. Navab M, Anantharamaiah GM, Reddy ST, et al. Potential clinical utility of high-density lipoprotein-mimetic peptides. Curr Opin Lipidol 2006;17:440–4.
73. Nissen SE, Tuzcu EM, Brewer HB, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. N Engl J Med 2006;354:1253–63.
74. Kastelein JJP, Wedel MK, Baker BF, et al. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. Circulation 2006;114:1729–35.
75. Frelinger AL 3rd, Furman MI, Linden MD, et al. Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-

dependent but cyclooxygenase-1- and cyclooxygenase-2-independent pathway: a 700-patient study of aspirin resistance. Circulation 2006; 113:2888–96.
76. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. Eur Heart J 2006;27:1166–73.
77. Borgdorff P, Tangelder GJ, Paulus WJ. Cyclooxygenase-2 inhibitors enhance shear stress-induced platelet aggregation. J Am Coll Cardiol 2006;48:817–23.
78. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation 2006;113:1578–87.
79. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706–17.
80. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367:1665–73.
81. Leger AJ, Jacques SL, Badar J, et al. Blocking the protease-activated receptor 1-4 heterodimer in platelet-mediated thrombosis. Circulation 2006;113:1244–54.
82. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006;27:1038–47.
83. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368:581–8.
84. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.
85. Campia U, Matuskey LA, Panza JA. Peroxisome proliferator-activated receptor-gamma activation with pioglitazone improves endothelium-dependent dilation in nondiabetic patients with major cardiovascular risk factors. Circulation 2006;113:867–75.